Remarks/Arguments:

These remarks are responsive to the Office Action dated January 6, 2009. References to paragraph numbers of the specification refer to the published application, US 2005/0020818.

Applicants thank the Examiner for the telephone interview of March 26, 2009. During the interview, it was agreed to cancel claim 7 and the claims dependent on claim 7, thus rendering the rejections of these claims moot. The Examiner also indicated that evidence specifically pointing out unobviousness of the remaining claims over Bonafe and Litt would be helpful with respect to overcoming the rejections based on those references.

Applicants acknowledge with thanks that rejections of claims 1-12 under Section 103(a) as unpatentable over Litt (US Pat. No. 6, 635,469) and Silva *J. Biol. Chem. 264*: 15863-15868, 1989) have been withdrawn.

Claims 1-12 stand rejected under 35 USC Section 112, second paragraph, as indefinite. As previously indicated, the rejection of claims 7-12 is moot. The rejection of claims 1-6 is traversed for reasons indicated below.

Applicants' claim 1 is directed to recovering native protein from a sample comprising *protein aggregates*. As acknowledged in the Office Action in paragraph 7, the specification explicitly defines "protein aggregates" as "not intended to include the normal association between subunits of a native multi-subunit protein complex or the normal association of capsomeres in a native viral particle." (paragraph [0030]). Thus, the association of subunits in native multi-subunit protein complexes such as hemoglobin and hemocyanin are excluded from the scope of the term "protein aggregates" and are not part of the claimed subject matter of claim 1 and claims 2-6, which depend from claim 1.

Accordingly, Applicants request that the Section 112 rejections of claims 1-6 be withdrawn.

Claims 1, 3, 7, and 8 stand rejected under 35 USC 102(b) as anticipated by Silva and Bonafe. As previously indicated, the rejection of claims 7 and 8 is moot. Applicants traverse the rejection of claims 1 and 3 for the following reasons.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP Section 2131 quoting *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Applicants' claims are directed to a method for recovering native refolded protein from a sample comprising protein aggregates. As discussed above, when construed according to the explicit definition of "protein aggregates" found in the specification, the protein aggregates of claims 1 and 3 do not encompass the association of native subunits of multi-subunit protein complexes.

As discussed in responses to previous office actions, Silva describes the effects of pressure on the association of subunits of native hemoglobin, a native multi-subunit protein complex. Bonafe, *Biochemistry 33*: 2651-2660, 1994, describes the effects of pressure on the association of native hemocyanin, which is also a native multi-subunit protein complex. As discussed above, Applicants have specifically excluded associations of subunits in native multi-subunit protein complexes from their definition of "protein aggregates."

In addition, neither Silva nor Bonafe discloses an effect of pressure on protein unfolding or refolding. In fact, both references teach that dissociated subunits of native oligomeric proteins remain in a native state with only minor, if any, conformational changes after dissociation from the oligomer. The maintenance of native subunits following dissociation of an oligomeric protein is a central tenet of the theory of "conformational drift" that is the focus of both the Silva and Bonafe references. Thus, these are native subunits of an oligomeric protein and are not unfolded, misfolded, or aggregated proteins.

For these reasons, neither Silva nor Bonafe can anticipate claims 1 and 3. Therefore, Applicants request that the Section 102(b) rejection of these claims be withdrawn.

Claims 1-12 stand rejected under 35 USC 103(a) as obvious over Bonafe and Litt. As previously indicated, the rejection of claims 7-12 is moot. Applicants traverse the rejection of claims 1-7 for the following reasons.

As discussed above, Bonafe discloses the effects of pressure on the association and dissociation of subunits of hemocyanin, a native multi-subunit protein complex. Bonafe does not teach the use of pressure to refold dissociated proteins from aggregates as required by claims 1-6. Litt cannot compensate for the elements missing in Bonafe. Litt teaches that aggregated proteins must be denatured and exposed to pressure cycling in order to refold the dissociated proteins. Neither Bonafe nor Litt discloses the use of pressure to dissociate proteins from protein aggregates in the absence of denaturing agents or pressure cycling, in order to refold a portion of the dissociated protein to native protein, as required by Applicants' claims.

Furthermore, one of skill in the art would not combine the method of Bonafe with the method of Litt, because they are contradictory. Bonafe states that "a method that permits controlled perturbation of the subunit interactions must be employed" to study the assembly of large multimeric proteins. To this end, Bonafe teaches conditions that do not denature the protein subunits (Bonafe, page 2651 and Figure 1A). In contrast, Litt teaches that protein aggregates must be denatured and subjected to pressure cycling to bring about proper protein refolding (Litt, Col. 9, lines 15-24). Combining Litt with Bonafe would defeat the purpose of Bonafe. One of ordinary skill in the art would have no reasonable expectation that controlled perturbation of subunit interactions could be achieved with denatured protein, and thus would have no motivation to combine Litt with Bonafe.

In addition, Applicants' claimed method results in unexpected and surprising results that could not have been predicted from Bonafe and Litt. This is clearly indicated in the Declaration of Dr. Anne Robinson, submitted herewith in accordance with 37 CFR § 1.132. As indicated in Dr. Robinson's Declaration and attached curriculum vitae, she is a Professor of Chemical Engineering at the University of Delaware and has worked in the field of protein refolding and renaturation for the past 15 years. Dr. Robinson has trained a number of graduate students and published widely in this field. This year, she is the Co-Chair of the 2009 Biochemical Engineering Conference which for many years has gathered the world's experts in the field of chemical engineering of biological systems.

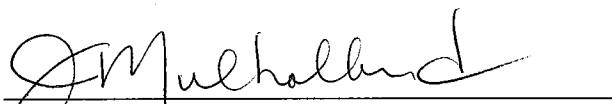
For these reasons it is not reasonable to conclude that the Bonafe and Litt references, either alone or in combination, render Applicants' claimed method obvious under a proper

reading of 35 USC Section 103(a). The rejection of claims 1-6 for obviousness over Bonafe and Litt should therefore be withdrawn.

Conclusion

It is respectfully submitted that the claims are in condition for immediate allowance and a notice to this effect is solicited. The Examiner is invited to phone applicants' attorney if it is believed that a telephonic interview would expedite prosecution of the application.

Respectfully submitted,



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Attachments:
Declaration of Anne Skaja Robinson
Appendix - Curriculum Vitae of Anne Skaja Robinson

Dated: March 31, 2009

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